

Changes in vigorous physical activity and incident diabetes in male runners

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Objective & Design: We examined the dose-response relationship between changes in reported vigorous exercise (running distance, $\Delta\text{km/wk}$) and self-reported physician diagnosed diabetes in 25,988 men followed prospectively for (mean \pm SD) 7.8 ± 1.8 years.

Results. Logistic regression analyses showed that the log odds for diabetes declined significantly in relation to men's $\Delta\text{km/wk}$ (coefficient \pm SE: -0.012 ± 0.004 , $P<0.01$), which remained significant when adjusted for BMI (-0.018 ± 0.003 , $P<0.0001$). The decline in the log odds for diabetes was related to the distance run at the end of follow-up when adjusted for baseline distance, with (-0.024 ± 0.005 , $P<0.0001$) or without (-0.027 ± 0.005 , $P<0.0001$) adjustment for BMI. Baseline distance was unrelated to diabetes incidence when adjusted for the distance at the end of follow-up. Compared to men who ran <8 km/wk at the end of follow-up, incidence rates in those who ran ≥ 8 km/wk were 95% lower between 35-44 yrs old ($P<0.0001$), 92% lower between 45-54 yrs old ($P<0.0001$), 87% lower between 55 and 64 years old ($P<0.0001$), and 46% lower between 65-75 yrs old ($P=0.30$). For the subset of 6,208 men who maintained the same running distance during follow-up (± 5 km/wk), the log odds for diabetes declined with weekly distance run (-0.024 ± 0.010 , $P=0.02$) but not when adjusted for BMI (-0.005 ± 0.010 , $P=0.65$).

Conclusion: Vigorous exercise significantly reduces diabetes incidence, due in part to the prevention of age-related weight gain and in part to other exercise effects.

Physical activity decreases the risk of type 2 diabetes [1-10]. Moderate and vigorous exercise are purported to produce comparable reductions in diabetes risk if the energy expenditure is the same [3,10]. The optimal physical activity dose remains unclear, however, with some [4-7] but not all studies [1,8,9] showing continued reduction in diabetes for high versus intermediate energy expenditures.

The National Runners' Health Study [11-19] is unique among population cohorts in its focus on the health impact of higher doses of vigorously intense physical activity (i.e., ≥ 6 -fold metabolic rate). The study was specifically designed to evaluate the dose-response relationship between vigorous physical activity and health for intensities and durations that exceed current physical activity recommendations [20-22]. One specific hypothesis is whether changes in vigorous physical activity affect the risk for becoming diabetic. Although women were surveyed and followed-up, only 23 developed diabetes so there is limited statistical power to establish their significance. Our analyses of diabetes and vigorous exercise are therefore restricted to men.

This paper relates running distance at baseline and at the end of follow-up to self-reported, physician diagnosed diabetes in vigorously active men who were generally lean and ostensibly at low diabetic risk. The benefits of greater doses of more vigorous exercise are relevant to the 27% of U.S. women and 34% of U.S. men meet or exceed the more general exercise recommendations for health benefits [23]. Specific issues to be addressed are: 1) whether maintenance of the same level of vigorous exercise over time reduces the risk of incident diabetes in relation to the exercise dose; 2) whether men who decrease their activity increase their risk for becoming diabetic; and 3) whether end of follow-up running distances are more predictive of diabetes than baseline distances, suggesting a causal, acute effect. Elsewhere we have shown that greater body weight is related to a lack of vigorous exercise [12-14] and increases the risk for diabetes even among generally lean vigorously active men [11]. In runners, leanness may be due to the exercise or due to initially lean men choosing to run further [17]. Therefore we also test whether body weight mediates the effects of vigorous exercise on diabetes, and whether this may be due to self-selection.

Methods

The survey instruments and baseline characteristics of the National Runners' Health Survey are described elsewhere [11-19]. Briefly, a two-page questionnaire, distributed nationally at races and to subscribers of a popular running magazine (Runners' World, Emmaus, PA), solicited information on demographics, running history, weight history, smoking habits, prior history of heart attacks and cancer, and medications for blood pressure, thyroid conditions, high cholesterol and diabetes. Recruitment took place between 1991 and 1994 (primarily 1993) and follow-up between 1999 and 2002. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. The study protocol was approved by the University of California Committee for the Protection of Human Subjects, and all participants signed committee-approved informed consents.

BMI was calculated as weight in kilograms divided by the square of height in meters. Elsewhere, we have reported the strong correlations between self-reported and clinically measured heights ($r=0.96$) and weights ($r=0.96$) [18], and for self-reported running distances versus self-reported BMIs in cross-sectional analyses [19]. Repeat questionnaires in 110 men also showed that self-reported body weights at the start running 12 or more miles per week had a correlation of 0.97. Physical activity was reported as average distance run per week. Although other leisure-time physical activities were not recorded for this cohort, data from runners recruited after 1998 (when the survey question was introduced) show that running represented (\pm SD) $91.5\pm19.1\%$ of all vigorously intense activity, and $73.5\pm23.7\%$ of total reported leisure-time physical activity. Self-reported distance run has been found to be reliable (test-retest correlations of $r=0.89$ [18]). Eighty percent of the 54,956 participants of the National Runners' Health Study provided follow-up information or were known deceased.

Participants reported whether a physician had told them they had diabetes since their baseline questionnaire, and whether they took medications for diabetes at baseline and the end of

follow-up. Incident diabetes is defined as physician diagnosis or starting medications for this condition subsequent to their baseline questionnaire.

Statistics We employed logistic regression analyses to test whether changes in distance run per week were related to the incidence of diabetes (JMP version 4, SAS Institute, Cary, NC). The results are presented simultaneously adjusted for BMI at the end of follow-up and at baseline (BMI_{exercise}), and adjustment for BMI when they first began running 12 or more miles per week ($BMI_{\text{pre-exercise}}$). Adjustment for $BMI_{\text{pre-exercise}}$ was compared to adjustment for BMI_{exercise} to assess whether the attenuating effect of the adjustment reflect BMI as a mediator (independent of $BMI_{\text{pre-exercise}}$) or as a self-selection effect (entirely due to $BMI_{\text{pre-exercise}}$). All results (except the descriptive results of Table 1) include adjustment for the average age during follow-up (age and age²), follow-up duration, and the average weekly intakes of alcohol, meat, fish, and fruit at baseline and at the end of follow-up. We also used logistic regression analyses to estimate the incidence of diabetes within five age intervals 18-35, 35-44, 45-54, 55-64, and 65-74, years old. Incident diabetes was used as the dependent variable and age intervals as the independent variables in a zero intercept logistic regression analyses, where an individual's log odds for developing diabetes was the sum of the time spent between the baseline and the end of follow-up survey within each interval [14].

Results

There were 29,140 men who were nonsmokers, nonvegetarian, and nondiabetic at baseline who provided baseline running distance, height and weight. From these we excluded 2,020 men who completed only one side of their follow-up survey questionnaire, 844 men who did not provide their end of follow-up running distance (which probably implies they had stopped running), and 288 men who did not report their end of follow-up BMI. Relative to the entire baseline cohort, those that were excluded ran similar weekly baseline distances (excluded vs. included mean \pm SE, 23.7 \pm 0.2 vs. 23.4 \pm 0.1 km/wk) and weighed the same (23.9 \pm 0.04 vs. 23.9 \pm 0.02 kg/m²) as those included in the analyses, but were significantly older (47.7 \pm 0.2 vs. 44.6 \pm 0.1 years), had run more years at baseline (13.8 \pm 0.1 vs. 13.1 \pm 0.1 years). The characteristics of the remaining sample, analyzed in this paper, are presented in

Table 1. The table shows that changes in weekly distance run were inversely associated with changes in BMI and the incidence of diabetes.

Table 2 shows that change in running distance was inversely related to the log odds for becoming diabetic (Model 1). Adjustment for BMI_{pre-exercise} had little effect. The greater the decline in running distance, the greater the increase in incidence. When adjusted for BMI_{exercise}, men who decreased their weekly running distance were at significantly greater odds for becoming diabetic than those who increased their distance by 8 km/wk or more (Figure 1, left panel).

Included in these analyses were 6,208 men who maintained their running distance within ± 5 km/wk during follow-up. These men's log odds for incident diabetes declined in proportion to their average weekly kilometers run (regression coefficient \pm SE: -0.024 ± 0.010 , $P<0.05$) even in the absence of any change in distance. The coefficient became nonsignificant when adjusted for BMI_{exercise} (-0.005 ± 0.010), whereas it remained essentially unchanged when adjusted for BMI_{pre-exercise} (-0.022 ± 0.010 , suggesting mediation rather than self-selection).

Table 3, model 2 considers an alternative formulation of the logistic regression used in Table 2, one that includes baseline and end of follow-up running distances directly, rather than their re-expression as their average and their difference.—The significance levels refer to the significance of the end of follow-up km/wk run when adjusted for baseline distance, and the significance of the baseline km/wk run when adjusted for the end of follow-up distance. The incidence of diabetes was inversely related to running distance at end of follow-up but not at baseline. Adjusting the end of follow-up distance for BMI_{exercise} or BMI_{pre-exercise} had little effect on the coefficient. Figure 2 (right panel) shows that end-of follow-up distances of 8 km/wk or more were associated with a 50% reduction in the odds for becoming diabetic compared to less active men.

Finally, the data were analyzed to assess the progressive increase in the risk of becoming diabetic with age. The data were stratified by running distances at the end of follow-up to test whether the incidence for <8 km/wk was different from the incidence at ≥ 8 km/wk. Running

distances ≥ 8 km/wk were combined because their graphs were largely overlapping. The log odds for incident diabetes for men < 35 years old, 35-44 years old, 45-54 years old, 55-64 years old were calculated within each stratum as described in Methods. These are presented in Figure 3 2 as incidence rates per 1000 person years. Among men 35 years and older, diabetes incidence was significantly lower for those who ran over 8 km/wk compared to those who ran less. The lack of significance in men < 35 years old simply reflect the smaller sample size and limited statistical power to detect differences.

Discussion

These analyses demonstrate that the odds for developing diabetes were significantly related to changes in weekly distance run in men. Men who increased their running distance by an average of 18 km/wk (i.e., the average distance run within the > 8 km/wk category of Figure 1, left) had significantly lower odds of becoming diabetic than those who decreased their distance run. The odds for developing diabetes appeared to be related to distances run at the end of the follow-up period only, suggesting that the effect of distance run on diabetes (or the converse) is acute. Because these analyses examine concurrent changes in vigorous exercise with diabetes incidence, they do not distinguish between whether running affects diabetes risk or conversely, diabetes affects the ability to run. However, among the 6,208 men who maintained the same level of vigorous exercise during follow-up, the odds for becoming diabetic declined in association with running distance. Table 2 and Figure 1 (right) appear to negate the possibility that the effect is due to self-selection, i.e., that men who are at higher risk for diabetes choose to run shorter distances, because this would be expected to affect baseline as well as follow-up running distances. This latter observation is important given our previous observations that 26% of the association between body weight and running distance, and all of the association between weight and cardiovascular fitness, can be ascribed to initially leaner men choosing to run further and faster [17].

The analyses of Figure 1 (left) would seem to suggest that the end of follow-up, running as little 8-16 km/wk reduces the odds for becoming diabetic. This agrees with other studies

showing that subjects who had intermediate physical activity levels were at lower risk than the most sedentary individuals [1-10]. Over the past decade, physical activity guidelines of the Centers for Disease Control and Prevention, National Institutes of Health and the American Heart Association have emphasized the health benefits of walking 2 miles (3.2 km) briskly on most days of the week [20-22]. A two-mile brisk walk five days per week is the energy equivalent of running 10.9 km/wk [24], thus these recommendations are consistent with Figure 2. The figure also suggests further reductions in the odds for developing diabetes accrue at still higher doses of vigorous exercise.

The age-specific analyses of Figure 2 shows significantly less diabetes in those who exceeded 8 km/wk (average 18 km/wk) compared to less active men throughout middle age and older. Men over 35 years old who were vigorously active had rates of incident diabetes comparable to young men. For diabetes and other cardiovascular risk factors [19], the benefits of vigorous exercise do not appear to be substantially diminished with age. In Figure 32, the decrease in incidence diabetes in 65-75 year old men vis-à-vis younger men who ran under 8 km/wk could simply be due to the greater imprecision of the estimate due to the small sample size, as reflected in the broad confidence interval.

One assumption of the traditional prospective design is that the probability of the event remains constant. As shown in Table 1, the majority of men decreased their activity during follow-up. Our analyses of the 6,208 men who maintained the same level of activity throughout follow-up represents the idealized prospective cohort study design. The decline in their log odds for diabetes per km/wk run (-0.024 ± 0.10 per km) was 71% larger than the logistic regression coefficient for the entire sample without regard to changes in running distance during follow-up (-0.014 ± 0.004 , $P < 0.001$, unpublished observation). This suggests that prospective studies of physical activity and diabetes may underestimate the true benefit of physical activity [1-10].

Although adjustment for BMI only moderately affected the relationships of Table 32, the adjustment did eliminate the relationship between diabetes and distance run among men who ran consistently during follow-up. Others also report that BMI adjustment attenuates the

relationship between physical activity and diabetes [10]. We have previously demonstrated in this same cohort of men, that baseline BMI predicts *de novo* diabetes during follow-up [11]. Normal-weight men who were diagnosed for diabetes during follow-up had higher BMIs and larger waist circumferences at baseline than those that remained nondiabetic [11]. Although the odds for diabetes accelerated much more dramatically at higher BMI levels, men with BMIs between 22.5 and 25.0 kg/m² were over twice as likely to become diabetic as leaner men [11]. At higher levels, the odds for diabetes tripled for each 2.5 kg/m² increment. Other published findings by us show that vigorous exercise attenuates age-related weight gain in men, and appears to be particularly efficacious in the prevention of more-extreme weight gain [14]. Changes in exercise levels in men also produces acute changes in body weight from increased and decreases in energy expenditure [13].

The principal limitations of these analyses are their reliance on self-reported diabetes, weekly running distances and body weights. The self-reported distance and weights appear reliable as indicated by their test-retest correlations [18], and their consistent relationships to other variables in this cohort [11-19]. The sample is generally college educated and therefore probably reliable in reporting physician diagnosis or medication use for diabetes. Hu et al reported that 88.6% of the Nurses Health Study who self-reported being diagnosed for diabetes were valid as determined from additional questions on classic symptoms, plasma glucose concentrations, or medication use to confirm type 2 diabetes [10]. This validity rate for the nurses may represent a upper bound on the error rate for our sample, which though educated are not generally medically trained. Evolving criteria for physician diagnosis of diabetes during the follow-up may affect incidence rates, there may be a tendency for individuals to underreport diagnosis due to privacy concerns, and the reliability of self-reported weight or exercise could have changed with age or over time, but we expect that such biases would be similar between high and low-mileage runners and therefore not affect the analyses. We have also reported that fasting plasma glucose levels from the medical records of 8,283 male runners declined significantly with distance run when compared cross-sectionally [19, 16]. Presumably few if any of the incident diabetes were type 1 since those using medication for diabetes at baseline were excluded from the analyses. Although insulin

use was reported by some runners who became diabetic, this would not necessarily be indicative of type 1 diabetes.

In summary, current public health guidelines are oriented on motivating sedentary and inadequately active men and women to include 30 minutes of moderately intense physical activity to their daily routine [20-22]. These recommendations appear apropos to the prevention of diabetes, however, greater exercise doses confer even greater health benefits. Other studies show that the exercise does not need to be vigorous to be beneficial; there is an accumulating body of evidence from randomized controlled studies, involving men and women with pre-diabetes status, that accumulation of 150 minutes per week of routine, lifestyle physical activity (particularly walking) can reduce the risks for type 2 diabetes [25-27] Future guidelines should discuss the health consequences of reducing activity in those who currently meet or exceed guideline levels:-

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Table 1. Characteristic of men who increased, maintained, or decreased weekly running distance					
	Increased distance		Decreased distance		
	>8 km/wk	8 to 0 km/wk	0 to -8 km/wk	-8 to -24 km/wk	<-24 km/wk
Males					
N	3560	4450	2609	8612	6756
% Diabetes (N)	0.31 (11)	0.63 (28)	0.96 (25)	0.63 (54)	0.81 (55)
Follow-up duration (years)	7.42±1.86	7.47±1.80	7.39±1.83	7.82±1.75	8.32±1.72
Average age (years)	46.62±9.77	48.78±9.95	49.83±9.94	49.22±10.01	47.64±10.87
Δkm/wk	17.89±14.72	1.30±2.06	-4.12±1.66	-13.38±4.43	-37.97±6.11
Average km/wk	38.55±20.80	29.37±20.09	23.50±17.16	30.28±19.11	34.30±19.27
ΔBMI (kg/m ²)	0.40±1.42	0.73±1.44	0.86±1.38	1.20±1.60	1.82±1.97
Education (years)	16.58±2.45	16.68±2.41	16.77±2.41	16.55±2.41	16.26±2.49
Meat (serving/wk)	2.87±3.29	2.99±3.18	2.93±3.07	2.92±3.16	2.99±3.56
Fish (serving/wk)	1.58±1.28	1.58±1.28	1.53±1.22	1.58±1.36	1.56±1.27
Fruit (serving/wk)	11.09±8.02	10.72±7.74	10.29±7.27	10.44±7.30	10.73±7.75
Alcohol (ml/wk)	77.93±100.77	85.84±105.64	85.82±108.34	88.32±105.15	87.08±111.26

Table 2. Logistic regression analyses of incident diabetes by running distance						
	Model 1 (Coefficients±SE)			Model 2 (Coefficients±SE)		
	Intercept	Δ km/wk	Average km/wk	Intercept	Baseline km/wk	Follow-up km/wk
Unadjusted	-4.354	-0.012 ±0.004†	-0.029 ±0.005§	-4.354	-0.002 ±0.005	-0.027 ±0.005§
BMI _{exercise} adjusted	-5.380	-0.018 ±0.003§	-0.012 ±0.005*	-5.380	0.013 ±0.004†	-0.024 ±0.005§
BMI _{pre-exercise} adjusted	-4.689	-0.009 ±0.004*	-0.025 ±0.005§	-4.689	-0.004 ±0.005	-0.022 ±0.005§
<p>Model 1 and 2 represent two approaches to entering the baseline and follow-up distances into the model, either separately as recorded or re-expressed as their difference and average. The intercept term includes the adjustment to the mean age, follow-up duration, and reported intakes of meat, fish, fruit, and alcohol. (Note, because the two models differ only in their expression of the baseline and follow-up values, the same intercept applies to both). Additional adjustment for BMI_{preexercise} (i.e., when they began running ≥12 km/wk) and BMI_{follow-up} (both baseline and end of follow-up BMI) as indicated. Significance levels for logistic regression coefficients are coded: * P<0.05, † P<0.01, ‡ P<0.001, § P<0.0001.</p>						

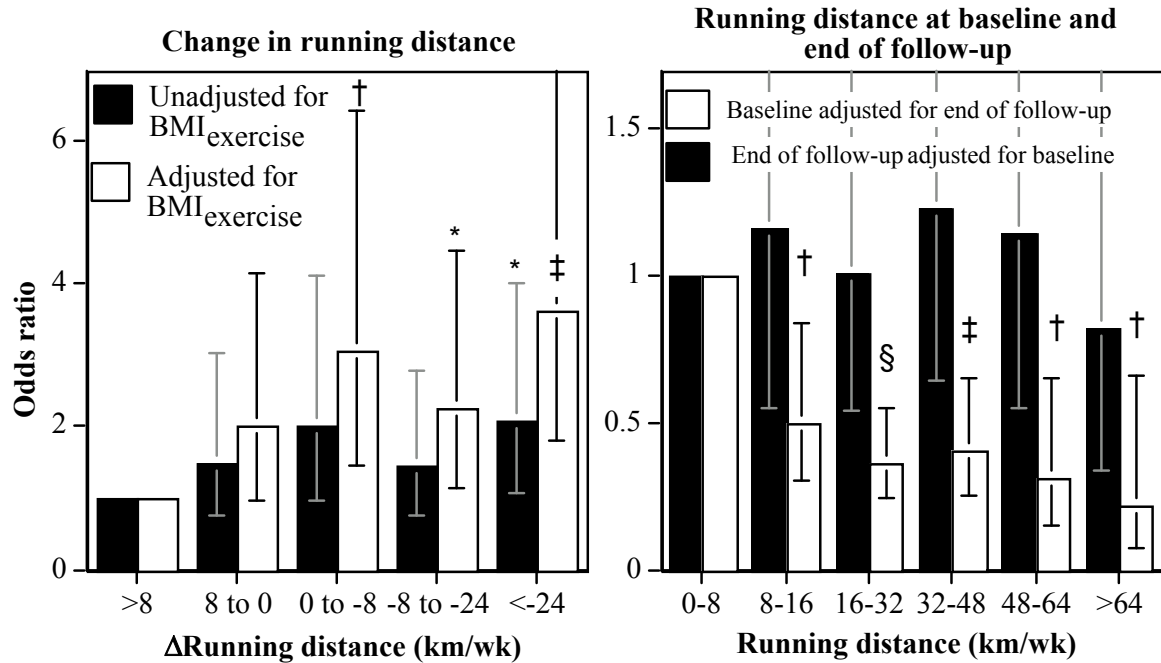


Figure 1. Odds ratio of incident diabetes in relation to concurrent changes in weekly running distance (left) and and baseline and follow-up distance (right) in 25,988 men during 7.8 years of follow-up. Adjusted for follow-up duration, and average age (age and age²), and average weekly intakes of meat, fish, and fruit during follow-up. Additional adjustment for BMI_{exercise} (BMI at baseline and at the end of follow-up) where indicated. Significant odds reductions relative to men averaging <16 km/wk (left) or 0-8 km/wk (right) are coded: * P<0.05; † P<0.01; and ‡ P<0.001.

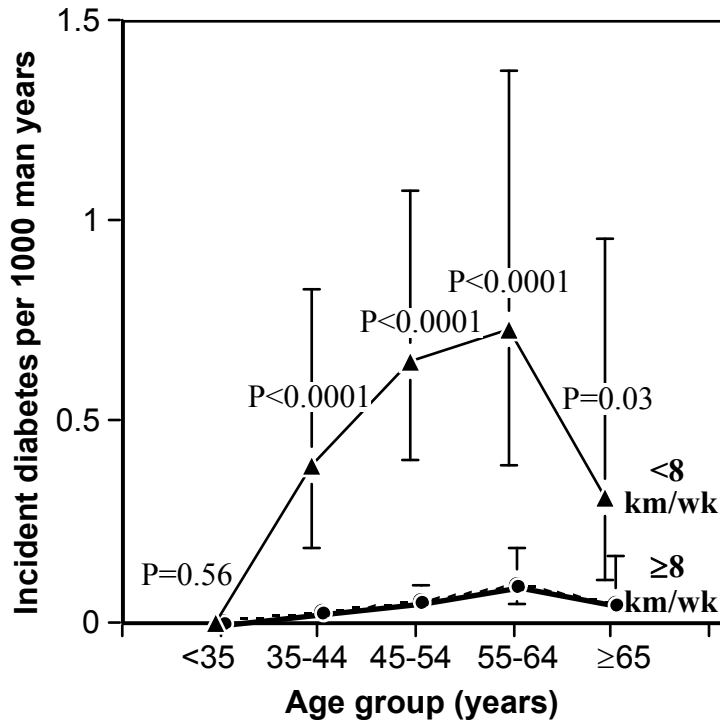


Figure 2. Incidence of diabetes by age classes and stratified by reported running distance (km/wk) at the end of follow-up. Person-years of follow-up for men who ran <8 km/wk and ≥ 8 km/wk, respectively, were 645 and 1,416 between 18 and 34 years old, 12,703 and 45,603 between 35 and 44 years old, 17,651 and 57,406 between 45 and 54 years old, 9,939 and 27,417 between 55 and 64 years old, and 3,469 and 7,532 between 65 and 74 years old.